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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,811	03/09/2006	Aaron Weinberg	200512.00033	5822

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EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
12/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/538,811	WEINBERG, AARON	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *14-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/21/06 and 6/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-13, in the reply filed on September 29, 2008 is acknowledged. Claims 1-37 are pending. Claims 14-37 are withdrawn from further consideration as they are drawn to non-elected inventions. Claims 1-13 are under examination.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on February 21, 2006 and June 1, 2006 are in compliance with the provisions of 37 CFR 1.97 and has been considered. An initialed copy is attached hereto. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

3. Claims 2-4 are objected to because of the following informalities: 1) Claims 2-4 recite non-elected inventions; and 2) In claim 4, the word "the" is repeated at the beginning of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to a defensin-stimulating composition, comprising a *Fusobacterium* associated defensin inducer (FAD-1) polypeptide and an excipient, wherein said FAD-1 polypeptide is selected from the group consisting of: a) a polypeptide that comprises an amino acid sequence that is at least 90% identical to the amino acid sequence selected from SEQ ID NO: 1; b) a polypeptide comprising a portion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce beta-defensin-2 or 3 (BD-2 or BD-3) production; and c) a composition comprising a *Fusobacterium* cell wall extract having a molecular weight range of 12-15 kDa which extract induces BD-2 or BD-3 production.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus of polypeptides or alternatively describe a representative

member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention.

A representative number of species means that the species which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The specification meets the Written Description requirements for SEQ ID NO: 1, however, the skilled artisan cannot envision the detailed chemical structure of the claimed polypeptides. The claims encompass a genus of polypeptides which are not adequately described. The recitation of at least 90% identical to SEQ ID NO: 1 represent a partial structure and the genus as claimed is highly variable. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. The specification is silent with regard to which polypeptide comprising an amino acid sequence at least 90%

identical to SEQ ID NO:1, or portion thereof and *Fusobacterium* cell wall extract will be sufficient to induce beta-defensin-2 and -3 production, particularly, defensin production in an epithelial cell, in the mouth, in the cornea and in the skin. The specification is equally silent with regard to which polypeptide comprises a potion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce BD-2 or BD-3 production.

Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al. (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Accordingly, it follows that the

functional domains associated with a given function can only be identified empirically. This constitutes undue experimentation

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential ability to bind a specific biological agent. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Further, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the

filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

The specification is equally silent with regard to which polypeptide comprises a potion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce BD-2 or BD-3 production.

5. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CRFC1988). The Wands factors have been considered in the establishment of this scope of enablement rejection. These factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claimed invention is directed to a defensin-stimulating composition, comprising a *Fusobacterium* associated defensin inducer (FAD-1) polypeptide and an excipient, wherein said FAD-1 polypeptide is selected from the group consisting of: a) a polypeptide that comprises an amino acid sequence that is at least 90% identical to the amino acid sequence selected from SEQ ID NO: 1; b) a polypeptide comprising a portion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce beta-defensin-2 or 3 (BD-2 or BD-3) production; and c) a composition comprising a *Fusobacterium* cell wall extract having a molecular weight range of 12-15 kDa which extract induces BD-2 or BD-3 production.

Breadth of the claims: The specification does not provide support for the claims as they are broadly drawn and encompass an unspecified amount of variants, fragments, portions, proteins within a cell wall extract and a plurality of polypeptides to induce beta-defensin-2 and -3 production, particularly, defensin production in an epithelial cell, in the mouth, in the cornea and in the skin.

Direction or guidance presented in the specification: The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The specification is silent with regard to which polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO:1, or portion thereof and *Fusobacterium* cell wall extract will be sufficient to induce beta-defensin-2 and -3 production, particularly, defensin production in an epithelial cell, in the

mouth, in the cornea and in the skin. Moreover, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation. Accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

Moreover, the specification is equally silent with regard to which polypeptide comprises a potion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce BD-2 or BD-3 production.

Presence or absence of working examples: There are no working examples provided to rectify the missing information in the instant specification pertaining to the claimed variants.

State of the prior art: The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al (J. Bacteriology, 2001; 183: 2405-2410) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (see page 2407, right column, page 2408, Fig. 3). The polypeptides of Seffernick et al are identical along relatively long stretches of their respective sequences (see page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the

Seffernick et al is small compared to those contemplated and encompassed by the claimed invention.

Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al. (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Accordingly, it follows that the functional domains associated with a given function can only be identified empirically. This constitutes undue experimentation

Quantity of experimentation necessary: The quantity of experimentation necessary would be undue as the claims encompass an unspecified amount of polypeptides having at least 90% sequence identity to SEQ ID NO: 1 and portions and

cell wall extracts thereof. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed genus. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidence by the state of the prior art, attempting the construct and test variants of the claimed invention would constitute undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is rendered vague and indefinite by the use of the phrase "cell wall extract". It is unclear what is meant by said phrase, as it is not explicitly defined in the specification. What constitutes a "cell wall extract"? The claims are drawn to an extract which comprises a multitude of proteins, but the claim refers to a range of the molecular weight of a single component of said extract. As written, it is impossible to determine

the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2 and 7-13 are rejected under 35 U.S.C. 102(b) as anticipated by Weinberg et al. (WO 99/64439).

The rejected claims are drawn to a defensin-stimulating composition, comprising a *Fusobacterium* associated defensin inducer (FAD-1) polypeptide and an excipient, wherein said FAD-1 polypeptide is selected from the group consisting of: a) a polypeptide that comprises an amino acid sequence that is at least 90% identical to the amino acid sequence selected from SEQ ID NO: 1; b) a polypeptide comprising a portion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce beta-defensin-2 or 3 (BD-2 or BD-3) production; and c) a composition comprising a *Fusobacterium* cell wall extract having a molecular weight range of 12-15 kDa which extract induces BD-2 or BD-3 production.

Weinberg et al. disclose compositions comprising defensin inducers and an aqueous carrier (see abstract and page 2). Weinberg et al. disclose that the inducer is isolated from the bacterial cell wall extract inducer of *Fusobacterium nucleatum* (see page 2). Weinberg et al. disclose that the composition enhances and/or induces

production of peptides, preferably defensins, more preferably α defensin and β defensin (see page 1; Summary of the Invention). Weinberg et al. disclose that the composition is administered in toothpaste, mouthwash, skin creams and cosmetic (eye cream) (see page 10). The claimed composition and the composition of Weinberg et al. are identical. Absent evidence to the contrary, the claimed composition necessarily stimulates defensin production in an epithelial cell, in the mouth, in the cornea and in the skin. Weinberg et al. necessarily meets the limitation of a polypeptide comprising a portion of an amino acid sequence selected from SEQ ID NO: 1, wherein said portion is sufficient to induce beta defensin-2 or -3 production.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
12/16/08

/Robert A. Zeman/
for Lakia J. Tongue, Examiner of Art Unit 1645